Registries in atrial fibrillation

Mazurek, Michał; Huisman, Menno V.; Lip, Gregory Y.h.

DOI:
10.1016/j.amjmed.2016.09.012

Document Version
Peer reviewed version

Citation for published version (Harvard):
Mazurek, M, Huisman, MV & Lip, GYH 2016, 'Registries in atrial fibrillation: from trials to real-life clinical practice', *The American Journal of Medicine*. https://doi.org/10.1016/j.amjmed.2016.09.012

Accepted Manuscript

Registries in Atrial Fibrillation: From Trials to Real-Life Clinical Practice

Michał Mazurek, MD, PhD, Menno V. Huisman, MD, PhD, Gregory Y.H. Lip, MD, PhD

PII: S0002-9343(16)31018-X

DOI: 10.1016/j.amjmed.2016.09.012

Reference: AJM 13728

To appear in: *The American Journal of Medicine*

Received Date: 29 July 2016

Revised Date: 8 September 2016

Accepted Date: 9 September 2016

Please cite this article as: Mazurek M, Huisman MV, Lip GYH, Registries in Atrial Fibrillation: From Trials to Real-Life Clinical Practice, *The American Journal of Medicine* (2016), doi: 10.1016/j.amjmed.2016.09.012.

REVIEW

Running Head: Registries on Atrial Fibrillation

Registries in Atrial Fibrillation:

From Trials to Real-Life Clinical Practice

Michał Mazurek, MD, PhD [a, b]
Menno V Huisman, MD, PhD [c]
Gregory Y H Lip, MD, PhD [a,d]

[a] University of Birmingham, Institute of Cardiovascular Sciences, City Hospital, Birmingham B18 7QH, United Kingdom; e-mail: g.y.h.lip@bham.ac.uk

[b] Department of Cardiology, Congenital Heart Diseases and Electrotherapy, Silesian Medical University, Silesian Centre for Heart Diseases, Zabrze, Poland; e-mail: m.i.c.h.a.l@wp.pl

[c] Department of Medicine-Thrombosis and Hemostasis, Leiden University Medical Center, Leiden, The Netherlands; e-mail: M.V.Huisman@lumc.nl

[d]Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark.

Correspondence:
Professor GYH Lip
University of Birmingham Institute of Cardiovascular Sciences, City Hospital, Birmingham B18 7QH, United Kingdom
Tel: +44 121 507 5080; Fax: +44 121 554 4083; E-mail: g.y.h.lip@bham.ac.uk

Funding: None.

Conflict of Interest: MM declared no conflict of interest. MVH has received honoraria for presentations as well as research grants from Boehringer Ingelheim, Bayer HealthCare, Pfizer, GlaxoSmithKline and Actelion Pharmaceuticals. GYHL has served as a consultant for Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Microlife and

Daiichi-Sankyo.Speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche and Daiichi-Sankyo.

Authorship: All authors had access to the data and played a role in writing this manuscript.

Clinical Significance

- There is wide variety of registries on atrial fibrillation with evident differences in design and methodology.
- Registry data demonstrate that despite gradual improvement in anticoagulation rates worldwide, there are apparent regional differences and gaps in stroke prevention with approximately a third of atrial fibrillation patients not treated in accord with guidelines.
- Remote mortality of atrial fibrillation patients is relatively high, while guideline-adherent antithrombotic therapy significantly reduces thromboembolism and improves survival.

ABSTRACT

Background

Recent improvements in atrial fibrillation diagnosis and management have prompted the initiation of various registries, predominantly to assess adherence to new guidelines, but also to address the pending questions of safety and effectiveness of newly introduced management options in 'real world' clinical practice settings. In this review we appraise antithrombotic treatment patterns for stroke prevention in atrial fibrillation registries.

Methods and Results

We searched PubMed, Science Direct and the Cochrane databases for registries focusing on stroke thromboprophylaxis in atrial fibrillation. Registry data show that over the last decade, the proportion of patients receiving oral anticoagulation has increased (from about 67% to over 80%), while the proportion of those treated with aspirin only or untreated has diminished. Vitamin K antagonists (VKAs) are being gradually replaced by non-VKA oral anticoagulants (NOACs) as the more prevalent option. Regional and country differences in anticoagulation are evident, with its highest uptake in Europe (90.2%) and lowest in Asia (57.4%). Moreover, oral anticoagulation is given to approximately 50% of patients with no stroke risk factors, whereas over a third of high-risk subjects are not anticoagulated but often prescribed antiplatelet therapy alone or untreated. Guideline non-adherent thromboprophylaxis results in an increase in all-cause mortality and thromboembolism.

Conclusions

Registry data show that despite an increase in anticoagulation rates over the last decade, management gaps in stroke prevention are still evident with about third of patients not treated in line with the guidelines. Mortality rates of atrial fibrillation patients remain relatively high, mostly due to the comorbid disease.

Keywords

Atrial fibrillation; Registry; Stroke prevention; Antithrombotic treatment

Over the last decade our knowledge of atrial fibrillation has substantially improved, mainly due to better understanding of epidemiology and pathophysiology of stroke and thromboembolism. As a consequence, new risk factors for stroke have been identified and our procedure for assessment of patients at risk has changed; formerly there was a tenacious search for patients at high thromboembolic risk, whereas now there is an effort to identify those individuals who are at truly low risk of stroke and do not need any antithrombotic treatment, so that stroke prevention can be focused on those with ≥1 stroke risk factors [1–6]. These changes coincided with the introduction of non-Vitamin K Antagonist oral anticoagulants (NOACs), which offer greater efficacy, safety and convenience compared with the Vitamin K Antagonists (VKAs, e.g. warfarin) [7–10].

Recently, several national and worldwide registries were initiated, predominantly to assess whether daily clinical practice is in accord with atrial fibrillation guidelines and to collect data on treatment with new drugs. Design and methodology of those registries vary substantially and have evolved over the last decade. This review provides an overview of past and current atrial fibrillation registries with respect to treatment patterns for stroke prophylaxis as well as aims to inform clinicians on the interpretation of results and limitations that may be inherent in different registry designs.

Methods

We searched PubMed, Science Direct and Cochrane Library databases for studies that reported on atrial fibrillation and stroke thromboprophylaxis. Multiple queries using following keywords were performed on July 1, 2016: (‘atrial fibrillation’ AND ‘registry’) AND (‘stroke prevention’ OR ‘antithrombotic treatment’ OR ‘oral anticoagulation’). We screened titles and abstracts for relevance to the topic. Articles of selected titles and abstracts were then reviewed for inclusion.

Purpose and Design of Various Observational Studies

There is considerable variety in registry design (Tables 1-3). National registries, like e.g. Swedish and Danish National Patient Registries, are ‘real time’ databases of the whole country population, where every patient is enrolled, every prescribed drug recorded, follow-up of patients is counted in years and vital status along with cause of death can be routinely

verified [11–13]. There are also international registries sponsored by learned societies, such as the EORP-AF (EURObservational Research Programme Atrial Fibrillation General Pilot Registry), which was initiated by the European Society of Cardiology (ESC), but its long-term extension to non-ESC countries continues by open collaboration, as part of the INTER-AF programme [14]. Moreover, there are academic-led registries from one single city or defined region, such as Fushimi AF (Table 1) [15,16].

In addition to large government sponsored databases, there are also several large, international, industry-sponsored registries (Table 2) such as GLORIA-AF (Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation) and GARFIELD-AF (Global Anticoagulant Registry in the FIELD) [17,18]. Some registries enroll only outpatients, such as ORBIT-AF (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation), J-RHYTHM or PINNACLE-AF (The American College of Cardiology Practice Innovation And Clinical Excellence Program), while others include only inpatients, e.g. Get With the Guidelines-AFIB (GWTG-AFIB) Registry [19–22]. Some of the registries are actually linked to specific programs to improve atrial fibrillation management. For example, the GWTG-AFIB is a United States (US) nationwide quality improvement program, which is intended not only to gather data, but also to provide a wide spectrum of health care sites with support to improve guideline adherence, arrhythmia management, and finally treatment outcomes [22]. There are also registries that record only baseline cross-sectional data [23,24]; though most have follow-up analyses. Registries have varying strategies to ensure data quality with some implementing rigorous standards, such as on site monitoring, extensive edit checks, frequent manual data reviews and periodic quality review of aggregate data. Others may not include such checks or make no mention of whether such standards were implemented, thus the measures taken to ensure data integrity should be considered when interpreting data.

Euro Heart Survey - Example of an 'Early' Non-Industry Sponsored Registry

Until 2005 there were no large scale European studies that prospectively collected data on atrial fibrillation epidemiology, management and outcomes. **Euro Heart Survey (EHS) on Atrial Fibrillation** was the first to verify routine clinical practice against the 2001 atrial fibrillation guidelines [25–27].

The registry enrolled 5333 in- and outpatients from 35 countries and reported oral anticoagulation (OAC) at 67%, with only 7% of patients not receiving any antithrombotic treatment. These were one of the highest OAC rates that were reported from a daily clinical practice in Europe [25,28,29]. Nevertheless, a discordance between guidelines and clinical practice was noted as 49% of ineligible patients received OAC, while 33% with an indication for anticoagulation were not treated as such [25].

Furthermore, prescription of OAC was only marginally guided by available stroke risk stratification schemes [26]. Importantly, the well-known risk factors for stroke were often not the trigger for anticoagulation, whilst other factors such as atrial fibrillation pattern (less OAC in paroxysmal arrhythmia) or availability of an anticoagulation monitoring clinic played a more predominant role in antithrombotic treatment decision making [26,30]. Multiplicity and complexity of risk stratifications schemes along with debates at that time on the importance of various risk factors for stroke such as hypertension or arrhythmia pattern, were some of the postulated reasons for guideline non-adherence [26,31,32].

In 2010, two new scoring systems were proposed - CHA_2DS_2VASc (congestive heart disease, hypertension, age ≥75 years [doubled], diabetes, stroke/TIA [transient ischemic attack]/systemic thromboembolism [doubled], vascular disease, age ≥65 years, sex category [female]) to assess stroke risk and HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding, labile international normalized ratio, age>65 years, drug/alcohol intake) for bleeding risk assessment [2,33,34]. Both scales are presently recommended by European and American guidelines [35–37].

10 Years Later – What Do We Know from Ongoing Registries Today?

Non-Industry Sponsored Registries

European Perspective

In 2012 the ESC established the **EORP-AF General Pilot Registry** to systematically collect contemporary data on atrial fibrillation treatment by cardiologists in Europe [14]. The registry enrolled 3119 in- and outpatients with atrial fibrillation diagnosed within the preceding year and shortly after first NOACs were on offer. This registry showed OAC use at 80.0% (71.6% VKAs and 8.4% NOACs), with 1/3 of patients receiving other antithrombotics (mostly aspirin) and 4.8% no antithrombotic treatment [38,39]. Surprisingly, OACs were used in 56.4%

of patients with CHA_2DS_2-VASc=0, whereas only 66.7% of those with CHA_2DS_2-VASc=9 were anticoagulated [38].

Guideline-adherent antithrombotic therapy was low at 61%, with 17.3% of patients being undertreated and 21.7% overtreated [40]. Importantly, antithrombotic management which was in line with the 2012 ESC guidelines, was associated with significantly better outcomes (all cause death/thromboembolic event of 9.0%), whereas the corresponding numbers for under- and overtreatment were 14.3% and 13.9% respectively [40].

One-year outcomes of EHS and EORP-AF Pilot Registry were strikingly similar. Mortality rates were 5.3% vs 5.7% respectively and the cause of death was cardiovascular in 67% vs 70%, respectively [41,42]. Death rates were highest in both registries in persistent/permanent atrial fibrillation, but also in a first-detected arrhythmia. However, one year stroke rates were higher in EHS than in EORP-AF (1.8% vs 0.6% respectively) [41,42]. Of note, in the EHS anticoagulation was discontinued in 45% of patients with no reoccurrence of arrhythmia and in 63% patients who were considered cured [42]. This is of importance, as undertreatment resulted in a 2-fold increase in thromboembolic events, compared with guideline-adherent management [30].

North American Perspective

OAC was low in the US outpatient registry sponsored by the American College of Cardiology (ACC) called **PINNACLE** [21]. This registry was a nationwide, prospective quality improvement program designed to capture, report and improve outpatient management in the pre-NOAC era. Between July 2008 and December 2009, the registry included 9113 patients from 20 US sites where overall OAC was only 55.1% [21]. These results showed a great variation in OAC prescribing across different US outpatient practices as well as near-random pattern of anticoagulation distribution [43]. In a larger analysis of 71,972 patients, subjects with paroxysmal atrial fibrillation were less commonly treated with OAC than those with persistent arrhythmia (50.4% vs. 64.3% respectively) but more frequently with antiplatelet therapy or no antithrombotic drugs [44]. In contrast, 26.6% with CHA_2DS_2-VASc=0 were prescribed OAC, despite having no indications for such treatment [45].

AF Registries Centred on Asia

Very low anticoagulation rates were reported from Asia, particularly China, where only approximately 20% of patients received OAC, while 40% were on aspirin and 40% untreated, resulting in an annual stroke risk of 9.28% [46–50]. By contrast, OAC was associated with annual stroke risk reduction by >50% and the adjusted net clinical benefit favouring OAC therapy over antiplatelet or no therapy for all patients with CHA_2DS_2-VASc score ≥1 [46,51–54]. In Japan, OAC rates are better than in China, though anticoagulation control is generally suboptimal. In the **J-RHYTHM Registry**, despite a high overall OAC at 87.3%, only 53% patients met target INR (International Normalized Ratio) levels [20,55–57].

Industry-Sponsored Registries

Suboptimal adherence to guidelines and regional differences in treatment patterns have been also observed in industry-sponsored registries.

GLORIA-AF is one of the largest, currently ongoing registries, that was initiated in 2011, and aims to enroll up to 56,000 patients from nearly 50 countries worldwide [17]. It has an innovative inception cohort design consisting of 3 overlapping phases (Figure 1 and Tables 2-3). The first phase of the study includes a period before NOAC introduction, the second phase begins immediately following approval of NOACs in a given country, and the third phase starts following propensity score comparisons in a region, between patient populations on VKA vs NOACs, to ensure baseline characteristics of those patients can be reasonably compared [17]. Such a registry design allows collection of data where there is dynamically changing clinical practice and available treatment methods with a reduced study bias. It also allows description of the pre-NOAC era [58] and the early period immediately following first NOAC approval [59], and can further inform about changing prescription patterns as the landscape of NOAC availability changes. It also implements a 'new user' design, which only includes incident cases of atrial fibrillation (diagnosed within the previous 3 months) to limit the potential for confounding factors such as disease co-morbidity [17,59].

Report from phase I (between May 2011 and January 2013) of GLORIA-AF showed OAC at 64.1% and 20.3% in Europe and China, respectively [58]. Though results of phase II (between November 2011 and February 2014) comprising over 10,000 patients were still showing regional differences in antithrombotic treatment patterns, the overall OAC uptake substantially increased to 80% (32.3% VKA and 47.7% NOAC) [59]. The highest OAC rates were observed in Europe at 90.2%, followed by 78.2% in North America and 57.4% in Asia

[59]. A considerable number of patients were still treated with antiplatelet therapy (5.7% in Europe, 14.1% in North America and 25.8% in Asia) or remained untreated (4.1% in Europe, 7.6% in North America and 16.9% in Asia).

GARFIELD-AF is another large scale, ongoing, international registry, initiated by the Thrombosis Research Institute, London [18]. The registry design is to enroll patients in 5 independent, sequential and prospective (but overlapping) cohorts and 4 of the cohorts enroll only subjects with newly diagnosed arrhythmia (Figure 2 and Tables 2-3) [18].

Data from the first out of five registry cohorts with 10,614 patients enrolled between 2009 and 2011 showed that 60.3% of patients received OAC (45.2% VKA alone, 4.5% NOAC), while 25.3% were given antiplatelet therapy alone and 14.4% did not use any antithrombotic drugs [60]. Contraindications to OAC were reported in only 7.8% of patients, yet 40.7% of eligible patients with a CHA_2DS_2-VASc score ≥2 were not given OAC, while in contrast 38.7% of those with a score of 0 received anticoagulation.

OAC uptake in GARFIELD-AF has improved over time. It was 57.4% in 2010 and increased to 71.1% in 2015. At the same time, NOAC uptake increased from 4.1% to 37% [61]. Importantly, the two-year all-cause mortality was 3.83 per 100 person-years and was far more frequent than the incidence of stroke or major bleeding (1.25 and 0.70 per 100 person-years, respectively) [62]. The cause of death was cardiovascular in 40.5% of cases and congestive heart failure with sudden cardiac death were responsible for 10.8% and 7.5% of deaths, respectively [62].

Comparing the Registries

Direct comparison of registries is not straightforward (Tables 1-3). There are different inclusion criteria for atrial fibrillation and its duration. For example, in GLORIA-AF and GARFIELD-AF only new onset arrhythmia (<6 weeks in GARFIELD-AF and <3 months in GLORIA-AF) is permitted, while it is <12 months in PREFER-AF and arrhythmia detected by implantable pacemaker/cardioverter-defibrillator is also allowed [17,18,63].

While most of the registries include only non-valvular atrial fibrillation, PREFER-AF or ORBIT-AF permitted also valvular arrhythmia [19,63]. GLORIA-AF requires at least one stroke

risk factor in CHA_2DS_2-VASc scale, while GARFIELD-AF does not use any stroke risk scales, enrolling patients with at least one risk factor at the discretion of physicians. PREFER-AF or ORBIT-AF enroll 'all comers', regardless of presence or absence of stroke risk factors [17,18,63]. To omit the influence of previous anticoagulation, GLORIA-AF excluded patients with a history of VKA therapy ≥60 days, whereas the rest of the registries are recruiting patients irrespective of previous or current OAC (Table 3).

Comparison of anticoagulation rates requires consideration of several factors, the most important of which seem to be the calendar year and time period of data collection. Indeed, OAC uptake is gradually, but constantly increasing worldwide and thus more recent reports show higher OAC rates [59,61]. However, registry design, regional contribution and availability of approved medications are also important (Table 3) [17,59]. Impact of site and setting may also play a role as e.g. registries from the region of Asia/Pacific may report lower OAC rates [59,60]. The proportions of in- and outpatients, academic institutions, participating physician specialties, patients of different ethnicities, different health care providers, and funding of the registries need to be also considered [59,60,63,64]. Indeed, in several registries, OAC was high where cardiologists were responsible for treatment [25,26,38,41,59,65]. When a broader spectrum of care settings was analyzed, including patients treated by other specialists, then the overall OAC was lower [60,66].

Finally, there are various atrial fibrillation guidelines issued by different organizations, which may differ with respect to stroke prevention recommendations [67]. American guidelines for example permit the use of aspirin or even no antithrombotic treatment in some patients (e.g. with CHA_2DS_2-VASc=1) [36].

Quo Vadis? Has Clinical Practice Changed?

Since the EHS over a decade ago (2003-2004), the overall use of OAC has increased, from 67% in EHS to 80.5% in EORP-AF (2012-2013), 82.3% in PREFER-AF (2012-2013), 80% in GLORIA-AF (2011-2014), and 71.1% in GAREFIELD-AF (2010-2015) [38,39,41,59,61,65]. Based on data from GLORIA-AF, NOACs are currently gradually replacing VKA both in Europe, where already more patients are prescribed NOACs, and in North America, when the usage of NOACs is twice as high as warfarin [59].

Possible reasons for an increase in OAC prescription over the last years may be increasing availability of NOACs, but also new guidelines and increased awareness of atrial fibrillation and stroke burden. This is also reflected by the falling number of patients being prescribed aspirin or those untreated [25,40]. Contemporary registries also demonstrate that by performance improvement efforts, any treatment gaps can be identified and bridged [38,39,41,59,61,65,68]. In the GWTG program, as a result of a tailored feedback and clinical decision support anticoagulation rates reached 95% [68].

However, despite best efforts, guideline-adherent thromboprophylaxis is still suboptimal. Indeed, approximately half of truly low-risk patients are overtreated with OAC, while a third of high risk patients are not anticoagulated [38,39,59,65]. Potential reasons are complex and include fear of bleeding complications, especially in certain patient populations (with low body weight, anemia, chronic kidney disease and the elderly), a perception that certain patterns of atrial fibrillation are more benign (paroxysmal or asymptomatic arrhythmia), subtherapeutic INR values, lack of good INR monitoring, and finally even cultural or habitual differences in treatment patterns [16,56,57,69–71].

Contraindications (approximately 10% of patients) and refusal to accept OAC are also important as these are often subjective and change over time [72]. These patients are generally older and more frail, with multiple comorbidities, but also at higher risk of stroke. In the ORBIT-AF registry, the most frequent reasons for warfarin forgoing were physician preference/choice (47.7%) and patient preference/refusal (21.1%) [60,73].

Conclusions

Though differences amongst registries on atrial fibrillation are evident, their main findings are similar and consistent thus giving us a very comprehensive insight into current clinical practice. Despite a gradual increase in anticoagulation rates worldwide, gaps in stroke prevention are still apparent, while guideline-adherent thromboprophylaxis improves outcomes [30,40]. Long-term mortality of atrial fibrillation patients is relatively high, exceeding both ischemic and bleeding events, mainly due to comorbid disease [41,42,62].

References

1. TAILLANDIER S, OLESEN JB, CLÉMENTY N, et al. Prognosis in Patients with Atrial Fibrillation and CHA2DS2-VASc Score = 0 in a Community-Based Cohort Study. *J Cardiovasc Electrophysiol*. 2012;23(7):708-713. doi:10.1111/j.1540-8167.2011.02257.x.

2. Lip GYH, Nieuwlaat R, Pisters R, Lane DA, Crijns HJGM. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest*. 2010;137(2):263-272. doi:10.1378/chest.09-1584.

3. Lip GYH, Lane DA. Stroke prevention in atrial fibrillation: a systematic review. 2015;313(19):1950-1962. doi:10.1001/jama.2015.4369.

4. Lip GYH, Skjoth F, Nielsen PB, Larsen TB. Non-valvular atrial fibrillation patients with none or one additional risk factor of the CHA2DS2-VASc score. A comprehensive net clinical benefit analysis for warfarin, aspirin, or no therapy. *Thromb Haemost*. 2015;114(4):826-834. doi:10.1160/TH15-07-0565.

5. Chao T-F, Liu C-J, Wang K-L, et al. Should Atrial Fibrillation Patients With 1 Additional Risk Factor of the CHA2DS2-VASc Score (Beyond Sex) Receive Oral Anticoagulation? *J Am Coll Cardiol*. 2015;65(7):635-642. doi:10.1016/j.jacc.2014.11.046.

6. Lip GYH, Nielsen PB. Should Patients with Atrial Fibrillation and 1 Stroke Risk Factor (CHA2DS2-VASc Score 1 in Men, 2 in Women) Be Anticoagulated?: Yes: even 1 Stroke Risk Factor Confers a Real Risk of Stroke. 2016;133(15):1498-1503. doi:10.1161/CIRCULATIONAHA.115.016713.

7. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361(12):1139-1151. doi:10.1056/NEJMoa0905561.

8. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365(10):883-891. doi:10.1056/NEJMoa1009638.

9. Granger CB, Alexander JH, McMurray JJ V, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365(11):981-992. doi:10.1056/NEJMoa1107039.

10. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2013;369(22):2093-2104. doi:10.1056/NEJMoa1310907.

11. Olesen JB, Lip GYH, Hansen ML, et al. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. *BMJ*. 2011;342:d124.

12. Friberg L, Skeppholm M, Terént A. Benefit of anticoagulation unlikely in patients with atrial fibrillation and a CHA2DS2-VASc score of 1. *J Am Coll Cardiol*. 2015;65(3):225-232. doi:10.1016/j.jacc.2014.10.052.

13. Staerk L, Lip GYH, Olesen JB, et al. Stroke and recurrent haemorrhage associated with antithrombotic treatment after gastrointestinal bleeding in patients with atrial fibrillation: Nationwide cohort STUDY. 2015;351. doi:10.1136/bmj.h5876.

14. Lip GYH. EUR Observational research programme: atrial fibrillation general registry pilot phase. *Eur Heart J*. 2013;34(11):794.

15. Akao M, Chun Y-H, Wada H, et al. Current status of clinical background of patients with atrial fibrillation in a community-based survey: the Fushimi AF Registry. *J Cardiol*. 2013;61(4):260-266. doi:10.1016/j.jjcc.2012.12.002.

16. Akao M, Chun Y-H, Esato M, et al. Inappropriate use of oral anticoagulants for patients with atrial fibrillation. *Circ J*. 2014;78(9):2166-2172.

17. Huisman M V, Lip GYH, Diener HC, et al. Design and rationale of Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation: a global registry program on long-term oral antithrombotic treatment in patients with atrial fibrillation. *Am Heart J*. 2014;167(3):329-334. doi:10.1016/j.ahj.2013.12.006.

18. Kakkar AK, Mueller I, Bassand JP, et al. International longitudinal registry of patients with atrial fibrillation at risk of stroke: Global Anticoagulant Registry in the FIELD (GARFIELD). 2012;163(1). doi:10.1016/j.ahj.2011.09.011.

19. Piccini JP, Fraulo ES, Ansell JE, et al. Outcomes registry for better informed treatment of atrial fibrillation: Rationale and design of ORBIT-AF. 2011;162(4). doi:10.1016/j.ahj.2011.07.001.

20. Atarashi H, Inoue H, Okumura K, Yamashita T, Origasa H. Investigation of optimal anticoagulation strategy for stroke prevention in Japanese patients with atrial

fibrillation-The J-RHYTHM Registry study design. 2011;57(1):95-99. doi:10.1016/j.jjcc.2010.09.002.

21. Chan PS, Oetgen WJ, Buchanan D, et al. Cardiac performance measure compliance in outpatients: the American College of Cardiology and National Cardiovascular Data Registry's PINNACLE (Practice Innovation And Clinical Excellence) program. *J Am Coll Cardiol*. 2010;56(1):8-14. doi:10.1016/j.jacc.2010.03.043.

22. Lewis WR, Piccini JP, Turakhia MP, et al. Get with the guidelines AFIB: Novel quality improvement registry for hospitalized patients with atrial fibrillation. 2014;7(5):770-777. doi:10.1161/CIRCOUTCOMES.114.001263.

23. Steg PG, Alam S, Chiang C-E, et al. Symptoms, functional status and quality of life in patients with controlled and uncontrolled atrial fibrillation: data from the RealiseAF cross-sectional international registry. *Heart*. 2011;98(3):195-201. doi:10.1136/heartjnl-2011-300550.

24. Gamra H, Murin J, Chiang CE, Naditch-Brûlé L, Brette S, Steg PG. Use of antithrombotics in atrial fibrillation in Africa, Europe, Asia and South America: Insights from the International RealiseAF Survey. 2014;107(2):77-87. doi:10.1016/j.acvd.2014.01.001.

25. Nieuwlaat R, Capucci A, Camm AJ, et al. Atrial fibrillation management: a prospective survey in ESC member countries: the Euro Heart Survey on Atrial Fibrillation. *Eur Heart J*. 2005;26(22):2422-2434. doi:10.1093/eurheartj/ehi505.

26. Nieuwlaat R, Capucci A, Lip GYH, et al. Antithrombotic treatment in real-life atrial fibrillation patients: A report from the Euro Heart Survey on Atrial Fibrillation. 2006;27(24):3018-3026. doi:10.1093/eurheartj/ehl015.

27. Fuster V, Rydén LE, Asinger RW, et al. ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guide. *Eur Heart J*. 2001;22(20):1852-1923. doi:10.1053/euhj.2001.2983.

28. Jackson SL, Peterson GM, Vial JH, Daud R, Ang SY. Outcomes in the management of atrial fibrillation: clinical trial results can apply in practice. *Intern Med J*. 2001;31(6):329-336.

29. Laguna P, Martn A, del Arco C, Gargantilla P. Risk factors for stroke and thromboprophylaxis in atrial fibrillation: what happens in daily clinical practice? The GEFAUR-1 study. *Ann Emerg Med*. 2004;44(1):3-11. doi:10.1016/S0196064404000587.

30. Nieuwlaat R, Olsson SB, Lip GYH, et al. Guideline-adherent antithrombotic treatment is associated with improved outcomes compared with undertreatment in high-risk patients with atrial fibrillation. The Euro Heart Survey on Atrial Fibrillation. 2007;153(6):1006-1012. doi:10.1016/j.ahj.2007.03.008.

31. Nieuwlaat R, Dinh T, Olsson SB, et al. Should we abandon the common practice of withholding oral anticoagulation in paroxysmal atrial fibrillation? *Eur Heart J*. 2008;29(7):915-922. doi:10.1093/eurheartj/ehn101.

32. Dagres N, Nieuwlaat R, Vardas PE, et al. Gender-related differences in presentation, treatment, and outcome of patients with atrial fibrillation in Europe: a report from the Euro Heart Survey on Atrial Fibrillation. *J Am Coll Cardiol*. 2007;49(5):572-577. doi:10.1016/j.jacc.2006.10.047.

33. Pisters R, Lane DA, Nieuwlaat R, De Vos CB, Crijns HJGM, Lip GYH. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: The euro heart survey. 2010;138(5):1093-1100. doi:10.1378/chest.10-0134.

34. Banerjee A, Marín F, Lip GYH. The improved but unfinished business of stroke risk stratification in atrial fibrillation. *Rev española Cardiol*. 2011;64(8):639-641. doi:10.1016/j.recesp.2011.04.005.

35. Camm AJ, Lip GYH, De Caterina R, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation--developed with the special contribution of the European Heart Rhythm Association. *Europace*. 2012;14(10):1385-1413. doi:10.1093/europace/eus305.

36. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *Circulation*. 2014;130(23):e199-e267. doi:10.1161/CIR.0000000000000041.

37. Atrial Fibrillation: The Management of Atrial Fibrillation - PubMed - NCBI. http://www.ncbi.nlm.nih.gov/pubmed/25340239. Accessed December 12, 2015.

38. Lip GYH, Laroche C, Dan GA, et al. A prospective survey in European Society of Cardiology member countries of atrial fibrillation management: Baseline results of EURObservational Research Programme Atrial Fibrillation (EORP-AF) Pilot General Registry. 2014;16(3):308-319. doi:10.1093/europace/eut373.

39. Lip GYH, Laroche C, Dan GA, et al. "Real-World" antithrombotic treatment in atrial fibrillation: The eorp-af pilot survey. 2014;127(6). doi:10.1016/j.amjmed.2013.12.022.

40. Lip GYH, Laroche C, Popescu MI, et al. Improved outcomes with European Society of Cardiology guideline-adherent antithrombotic treatment in high-risk patients with atrial fibrillation: A report from the EORP-AF General Pilot Registry. 2015;17(12):1777-1786. doi:10.1093/europace/euv269.

41. Lip GYH, Laroche C, Ioachim PM, et al. Prognosis and treatment of atrial fibrillation patients by European cardiologists: One Year Follow-up of the EURObservational Research Programme-Atrial Fibrillation General Registry Pilot Phase (EORP-AF Pilot registry). 2014;35(47):3365-3376. doi:10.1093/eurheartj/ehu374.

42. Nieuwlaat R, Prins MH, Le Heuzey J-Y, et al. Prognosis, disease progression, and treatment of atrial fibrillation patients during 1 year: follow-up of the Euro Heart Survey on atrial fibrillation. *Eur Heart J*. 2008;29(9):1181-1189. doi:10.1093/eurheartj/ehn139.

43. Chan PS, Maddox TM, Tang F, Spinler S, Spertus JA. Practice-level variation in warfarin use among outpatients with atrial fibrillation (from the NCDR PINNACLE program). *Am J Cardiol*. 2011;108(8):1136-1140. doi:10.1016/j.amjcard.2011.06.017.

44. Hsu JC, Chan PS, Tang F, Maddox TM, Marcus GM. Differences in anticoagulant therapy prescription in patients with paroxysmal versus persistent atrial fibrillation. *Am J Med*. 2015;128(6):654.e1-e654.e10. doi:10.1016/j.amjmed.2014.11.035.

45. Hsu JC, Chan PS, Tang F, Maddox TM, Marcus GM. Oral Anticoagulant Prescription in Patients With Atrial Fibrillation and a Low Risk of Thromboembolism: Insights From the NCDR PINNACLE Registry. *JAMA Intern Med*. 2015;175(6):1062-1065. doi:10.1001/jamainternmed.2015.0920.

46. Siu C-W, Lip GYH, Lam K-F, Tse H-F. Risk of stroke and intracranial hemorrhage in

9727 Chinese with atrial fibrillation in Hong Kong. *Heart Rhythm*. 2014;11(8):1401-1408. doi:10.1016/j.hrthm.2014.04.021.

47. Wang C, Yang Z, Wang C, et al. Significant underuse of warfarin in patients with nonvalvular atrial fibrillation: Results from the China National Stroke Registry. 2014;23(5):1157-1163. doi:10.1016/j.jstrokecerebrovasdis.2013.10.006.

48. Yang X, Li Z, Zhao X, et al. Use of Warfarin at Discharge Among Acute Ischemic Stroke Patients With Nonvalvular Atrial Fibrillation in China. *Stroke*. 2016;47(2):464-470. doi:10.1161/STROKEAHA.115.011833.

49. Kim WJ, Park JM, Kang K, et al. Adherence to Guidelines for Antithrombotic Therapy in Patients with Atrial Fibrillation According to CHADS2 Score before and after Stroke: A Multicenter Observational Study from Korea. *J Clin Neurol*. 2016;12(1):34-41.

50. Chen P-C, Lip GYH, Yeh G, Lin H-J, Chien K-L. Risk of bleeding and stroke with oral anticoagulation and antiplatelet therapy in patients with atrial fibrillation in Taiwan: a nationwide cohort study. *PLoS One*. 2015;10(4):e0125257. doi:10.1371/journal.pone.0125257.

51. Huang D, Anguo L, Yue W-S, Yin L, Tse H-F, Siu C-W. Refinement of ischemic stroke risk in patients with atrial fibrillation and CHA2 DS2 -VASc score of 1. *Pacing Clin Electrophysiol*. 2014;37(11):1442-1447. doi:10.1111/pace.12445.

52. Chao T-F, Liu C-J, Chen S-J, et al. Atrial Fibrillation and the Risk of Ischemic Stroke: Does It Still Matter in Patients With a CHA2DS2-VASc Score of 0 or 1? *Stroke*. 2012;43(10):2551-2555. doi:10.1161/STROKEAHA.112.667865.

53. Siu C-W, Tse H-F. Net clinical benefit of warfarin therapy in elderly Chinese patients with atrial fibrillation. *Circ Arrhythm Electrophysiol*. 2014;7(2):300-306. doi:10.1161/CIRCEP.113.000858.

54. Chen T, Yang Y-M, Tan H-Q, Liang Y, Zhu J. Baseline characteristics and 1-year follow-up of Chinese atrial fibrillation patients according to age: a registry study. *Pacing Clin Electrophysiol*. 2014;37(10):1392-1403. doi:10.1111/pace.12443.

55. Determinants of warfarin use and international normalized ratio levels in atrial fibrillation patients in Japan. - Subanalysis of the J-RHYTHM Registry-. *Circ J*. 2011;75(10):2357-2362.

56. Atarashi H, Inoue H, Okumura K, Yamashita T, Kumagai N, Origasa H. Present status of anticoagulation treatment in Japanese patients with atrial fibrillation: a report from the J-RHYTHM Registry. *Circ J*. 2011;75(6):1328-1333.

57. Inoue H, Okumura K, Atarashi H, et al. Target international normalized ratio values for preventing thromboembolic and hemorrhagic events in Japanese patients with non-valvular atrial fibrillation: results of the J-RHYTHM Registry. *Circ J*. 2013;77(9):2264-2270.

58. Huisman M V, Ma CS, Diener H-C, et al. Antithrombotic therapy use in patients with atrial fibrillation before the era of non-vitamin K antagonist oral anticoagulants: the Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation (GLORIA-AF) Phase I cohort. *Europace*. June 2016. doi:10.1093/europace/euw073.

59. Huisman M V., Rothman KJ, Paquette M, et al. Antithrombotic treatment patterns in patients with newly diagnosed nonvalvular atrial fibrillation: The GLORIA-AF Registry, phase II. In: Vol 128. Elsevier Inc.; 2015:1306-1313e1. doi:10.1016/j.amjmed.2015.07.013.

60. Kakkar AK, Mueller I, Bassand J-P, et al. Risk profiles and antithrombotic treatment of patients newly diagnosed with atrial fibrillation at risk of stroke: perspectives from the international, observational, prospective GARFIELD registry. *PLoS One*. 2013;8(5):e63479. doi:10.1371/journal.pone.0063479.

61. Kakkar AK. (2015, August). Anticoagulation and AF: real life data from the GARFIELD-AF registry. In: *Symposium Conducted at ESC Congress 2015, London, United Kingdom.*

62. Bassand J-P, Accetta G, Camm AJ, et al. Two-year outcomes of patients with newly diagnosed atrial fibrillation: results from GARFIELD-AF. *Eur Heart J*. June 2016. doi:10.1093/eurheartj/ehw233.

63. Kirchhof P, Ammentorp B, Darius H, et al. Management of atrial fibrillation in seven European countries after the publication of the 2010 ESC Guidelines on atrial fibrillation: Primary results of the PREvention of thromboemolic events-European Registry in Atrial Fibrillation (PREFER in AF). 2014;16(1):6-14. doi:10.1093/europace/eut263.

64. Steinberg BA, Kim S, Thomas L, et al. Lack of concordance between empirical scores

and physician assessments of stroke and bleeding risk in atrial fibrillation: Results from the outcomes registry for better informed treatment of atrial fibrillation (ORBIT-AF) registry. 2014;129(20):2005-2012. doi:10.1161/CIRCULATIONAHA.114.008643.

65. De Caterina R, Ammentorp B, Darius H, et al. Frequent and possibly inappropriate use of combination therapy with an oral anticoagulant and antiplatelet agents in patients with atrial fibrillation in Europe. 2014;100(20):1625-1635. doi:10.1136/heartjnl-2014-305486.

66. Fosbol EL, Holmes DN, Piccini JP, et al. Provider specialty and atrial fibrillation treatment strategies in United States community practice: findings from the ORBIT-AF registry. *J Am Heart Assoc*. 2013;2(4):e000110. doi:10.1161/JAHA.113.000110.

67. Camm AJ, Pinto FJ, Hankey GJ, Andreotti F, Hobbs FDR. Non-vitamin K antagonist oral anticoagulants and atrial fibrillation guidelines in practice: barriers to and strategies for optimal implementation. *Europace*. 2015;17(7):1007-1017. doi:10.1093/europace/euv068.

68. Lewis WR, Fonarow GC, Grau-Sepulveda M V, et al. Improvement in use of anticoagulation therapy in patients with ischemic stroke: results from Get With The Guidelines-Stroke. *Am Heart J*. 2011;162(4):692-699.e2. doi:10.1016/j.ahj.2011.07.019.

69. Hamatani Y, Yamashita Y, Esato M, et al. Predictors for Stroke and Death in Non-Anticoagulated Asian Patients with Atrial Fibrillation: The Fushimi AF Registry. *PLoS One*. 2015;10(11):e0142394. doi:10.1371/journal.pone.0142394.

70. Yamashita Y, Hamatani Y, Esato M, et al. Low Body Weight Is Associated With the Incidence of Stroke in Atrial Fibrillation Patients - Insight From the Fushimi AF Registry. *Circ J*. 2015;79(5):1009-1017. doi:10.1253/circj.CJ-14-1245.

71. Suzuki S, Yamashita T, Okumura K, et al. Incidence of ischemic stroke in Japanese patients with atrial fibrillation not receiving anticoagulation therapy--pooled analysis of the Shinken Database, J-RHYTHM Registry, and Fushimi AF Registry. *Circ J*. 2015;79(2):432-438. doi:10.1253/circj.CJ-14-1131.

72. O'Brien EC, Holmes DN, Ansell JE, et al. Physician practices regarding contraindications to oral anticoagulation in atrial fibrillation: findings from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) registry. *Am Heart J*. 2014;167(4):601-609.e1. doi:10.1016/j.ahj.2013.12.014.

73. O'Brien EC, Simon DN, Allen LA, et al. Reasons for warfarin discontinuation in the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). *Am Heart J*. 2014;168(4):487-494. doi:10.1016/j.ahj.2014.07.002.

74. Russo V, Bianchi V, Cavallaro C, et al. Efficacy and safety of dabigatran in a "real-life" population at high thromboembolic and hemorrhagic risk: Data from MonaldiCare registry. 2015;19(20):3961-3967.

75. Schwamm LH, Fonarow GC, Reeves MJ, et al. Get With the Guidelines-Stroke is associated with sustained improvement in care for patients hospitalized with acute stroke or transient ischemic attack. *Circulation*. 2009;119(1):107-115. doi:10.1161/CIRCULATIONAHA.108.783688.

76. Lewis WR, Fonarow GC, LaBresh KA, et al. Differential use of warfarin for secondary stroke prevention in patients with various types of atrial fibrillation. *Am J Cardiol*. 2009;103(2):227-231. doi:10.1016/j.amjcard.2008.08.062.

77. Hess CN, Peterson ED, Peng SA, et al. Use and Outcomes of Triple Therapy Among Older Patients With Acute Myocardial Infarction and Atrial Fibrillation. *J Am Coll Cardiol*. 2015;66(6):616-627. doi:10.1016/j.jacc.2015.05.062.

78. Okumura K, Inoue H, Atarashi H, et al. Validation of CHA_2DS_2-VASc and HAS-BLED scores in Japanese patients with nonvalvular atrial fibrillation: an analysis of the J-RHYTHM Registry. *Circ J*. 2014;78(7):1593-1599.

79. Tomita H, Okumura K, Inoue H, et al. Validation of Risk Scoring System Excluding Female Sex From CHA2DS2-VASc in Japanese Patients With Nonvalvular Atrial Fibrillation – Subanalysis of the J-RHYTHM Registry. *Circ J*. 2015;79(8):1719-1726. doi:10.1253/circj.CJ-15-0095.

80. Yamashita Y, Hamatani Y, Esato M, et al. Clinical characteristics and outcomes in extreme elderly (age ≥85) Japanese patients with atrial fibrillation: The Fushimi AF Registry. *Chest*. 2016;149(2):401-412. doi:10.1378/chest.15-1095.

81. Chao T-F, Wang K-L, Liu C-J, et al. Age Threshold for Increased Stroke Risk Among Patients With Atrial Fibrillation. *J Am Coll Cardiol*. 2015;66(12):1339-1347. doi:10.1016/j.jacc.2015.07.026.

82. Camm AJ, Kirchhof P, Lip GYH, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European

Society of Cardiology (ESC). *Europace*. 2010;12(10):1360-1420. doi:10.1093/europace/euq350.

83. Le Heuzey JY, Ammentorp B, Darius H, et al. Differences among western European countries in anticoagulation management of atrial fibrillation: Data from the PREFER IN AF Registry. 2014;111(5):833-841. doi:10.1160/TH13-12-1007.

84. Steinberg BA, Kim S, Piccini JP, et al. Use and associated risks of concomitant aspirin therapy with oral anticoagulation in patients with atrial fibrillation: insights from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) Registry. *Circulation*. 2013;128(7):721-728. doi:10.1161/CIRCULATIONAHA.113.002927.

85. Steinberg BA, Holmes DN, Piccini JP, et al. Early adoption of dabigatran and its dosing in US patients with atrial fibrillation: results from the outcomes registry for better informed treatment of atrial fibrillation. 2013;2(6).

86. Freeman J V, Simon DN, Go AS, et al. Association Between Atrial Fibrillation Symptoms, Quality of Life, and Patient Outcomes: Results From the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). *Circ Cardiovasc Qual Outcomes*. 2015;8(4):393-402. doi:10.1161/CIRCOUTCOMES.114.001303.

87. Steinberg BA, Blanco RG, Ollis D, et al. Outcomes registry for better informed treatment of atrial fibrillation II: Rationale and design of the ORBIT-AF II registry. 2014;168(2):160-167. doi:10.1016/j.ahj.2014.04.005.

Figure legend

Figure 1

Design of the GLORIA-AF Registry [17]

M – month; YR – year

Figure 2

GARFIELD Registry Design [18]

TABLES

Registries in Atrial Fibrillation:

From Trials to Real-Life Clinical Practice

Table 1 Non-Industry Sponsored Registries

Registry	Size (n)	Start date	Inclusion criteria	Follow-up	Design	Country	Comment
Euro Heart Survey on AF [25–28,30–32]	5333	2003	AF confirmed by ECG within 1 year before diagnosis, inpatients/ outpatients	1 year	Prospective observational	35 European countries	First large prospective registry assessing AF management against 2001 ACC/AHA/ESC guidelines; AF undertreatment results in a 2-fold increase in thromboembolism; Need for simple stroke/bleeding risk scale
ESC EORP AF Pilot [14,38,40–42]	3119	2012	AF confirmed by ECG within 1 year before diagnosis, inpatients/ outpatients	1 year	Prospective, consecutive, observational	9 EU countries	Non-adherence to 2012 ESC AF guidelines increases mortality; Antithrombotic overtreatment of low risk patients (with CHA_2DS_2-VASc=0) and undertreatment of high risk patients (1/3 on antiplatelet therapy)
PINNACLE-AF (National Cardiovascular Data Registry) [21,43–45]	>121000	2008	AF, outpatients	ongoing	National prospective, office-based, cardiac quality improvement registry	US	Antithrombotic overtreatment of low risk AF pts; Undertreatment of paroxysmal AF pts with moderate to high risk scores
Get With the Guidelines-AFIB (National Cardiovascular Data Registry) [22,68,75,76]	>5 million pts	2013	AF, inpatients	ongoing	Part of the national prospective, cardiac quality improvement programme	US	Large data registry; Support for healthcare providers and patients; Antithrombotic undertreatment of pts with AF and stroke
Get With the Guidelines-ACTION Registry (National Cardiovascular Data Registry) [77]	4959	2007	Acute myocardial infarction and AF	2 years	National prospective, cardiac quality improvement programme	US	Triple therapy (DAPT plus warfarin) vs DAPT in AF patients after acute myocardial infarction increases major bleeding with no difference in composite myocardial infarction, death or stroke
J-RHYTHM [20,55–57,78,79]	7937	2009	AF, outpatients	2 years	National, prospective, observational	Japan	OAC in sub-therapeutic doses; narrow INR values (1.6 and 2.59); female gender not an independent risk factor for stroke;
Fushimi [15,16,69–71,80]	3304	2011	AF, inpatients/ outpatients	2 years	community-based survey of consecutive AF patients	Japan, Kyoto	Kyoto region registry; high representation of private clinics of general practitioners; Overall OAC rate at 53.1% and therapeutic INR at 54.4% resulting in non-different outcomes between OAC and non-

							OAC users.
Nationwide Danish AF cohort [11,13]		1996	AF, inpatients/ outpatients	ongoing	National Patient Register; Consecutive AF patients	Denmark	Extensive data on all hospital admissions in Denmark since 1977. Civil registration system holds information on vital status of all citizens
Nationwide Swedish AF Cohort [12]		2005	AF, inpatients/ outpatients	ongoing	National Patient Register; Retrospective, unselected AF patients	Sweden	Extensive national data for all patients since 1997
Nationwide Taiwan AF Cohort [50,81]		1999	AF, inpatients/ outpatients	ongoing	National Patient Register; Retrospective, unselected AF	Taiwan	Extensive national data for all patients since 1996

AF = Atrial Fibrillation, ACC = American College of Cardiology, AHA = American Heart Association, DAPT = Dual Antiplatelet Therapy, ESC = European Society of Cardiology, EU = European Union, INR = International Normalized Ratio, OAC = Oral Anticoagulation, pts = patients, US = United States,

Table 2 Pharma-Industry Sponsored Registries

Registry	Size (n)	Start date	Inclusion criteria	Follow-up	Design	Country	Comment
RealiseAF Survey [23,24]	10,523	2009	AF confirmed by ECG within 1 year before diagnosis	Cross-sectional observation only	Cross-sectional observational survey; Participating physicians randomly selected from physician list forms	831 sites in 26 countries and four continents	Great regional differences in OAC uptake; Overuse or underuse of antithrombotics in approximately 50% of pts
GLORIA-AF [17,58,59]	56,000	2011	New AF diagnosis - within 3 months, CHA_2DS_2-VASc ≥1	3 years in phase III	Prospective, inception cohort design, 3 phases: 1. Pre-NOAC 2. With NOAC 3. Propensity comparison of pts on VKA vs NOAC	5 regions, >1000 sites in 50 countries	Strong design through increased comparability and minimized bias; high representativeness; 27000 patients to date; Broad physician representation; More than 1/5 of patients in North America and 1/3 in Asia under- or not treated with OAC
GARFIELD-AF [18,60–62]	57,000	2009	New AF diagnosis - within 6 weeks, at least 1 risk factor by physician assessment	Minimum 2 years, up to 8 years	Parallel enrollment of 5 prospective cohorts of unselected, consecutive patients with 1 retrospective validation cohort; 5 overlapping phases	1048 sites in 32 countries	Over 49000 pts enrolled; C1-4 complete C5 since Aug 2015 CHA_2DS_2-VASc 3.2; Broad spectrum of care-settings; Overtreatment of low-risk patients and undertreatment of high-risk ones; ½ of patients at moderate to high stroke risk not treated with OAC due to physician decision
PREFER-AF [63,65,82,83]	7243	2012	History of AF within the preceding 12 months, inpatients/outpatients	1 year	prospective	461 sites in 7 West and South Europe countries	AF management against 2010 guidelines; valvular AF not excluded; tendency towards a higher use of OAC in patients with higher stroke risk scores; substantial regional differences in OAC uptake
ORBIT-AF I [19,64,66,84–86]	10,126	2009	Incident + prevalent AF, outpatients	3 years	Prospective, ambulatory-based	184 US outpatient practices	$CHADS_2$ score 2.3; valvular AF not excluded; Includes cost and quality of life assessment; Broad spectrum of health care providers; higher use of OAC in patients with higher stroke risk scores;

							Discrepancy in OAC prescription amongst different care providers
ORBIT-AF II [87]	15,000	2013	New AF diagnosis (within 6 months) or/and initiation or transitioned to NOACs within the last 3 months	2 years	Prospective, ambulatory-based	300 US outpatient practices	Main focus on safety and effectiveness of NOACs (dosing, temporary interruptions, perioperative and bleeding management) used in community practice settings

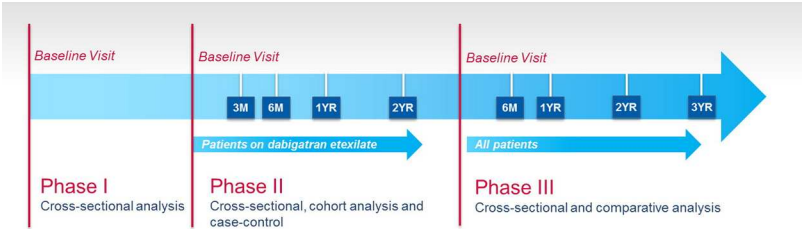
AF = atrial fibrillation, OAC = oral anticoagulation, NOAC = non-vitamin K oral antagonist, pts = patients, US = United States

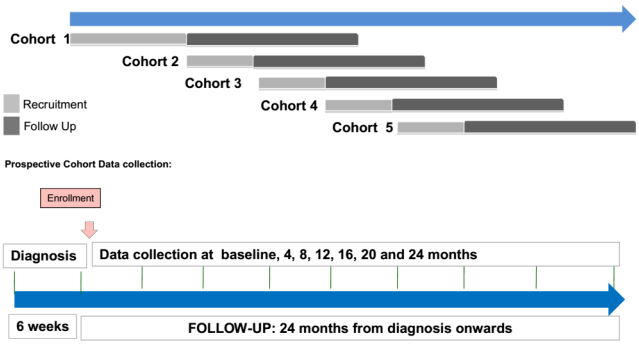
Table 3 Comparison of Registries Supported by Pharma Industry

	GLORIA-AF (Phase II, n=10871) [59]	**GARFIELD** (Cohort 1, n=10614) [60,61]	**PREFER-AF** (n=7243) [63]	**ORBIT-AF I** (n=10097) [66]	**ORBIT AF II** (n=1011) [87]
Site	International including US	International excluding US	International excluding US	US only	US only
Setting	Inpatients/outpatients (broad spectrum of settings)	Inpatients/outpatients	Inpatients/outpatients	Outpatients only	Outpatients only (academic and private clinics)
Physicians	Cardiologists/neurologists/internists/ geriatricians/GPs; 92% of patients enrolled by cardiologists	Cardiologists/neurologists/internists/ Geriatricians/GPs; 59% of patients enrolled by cardiologists	Cardiologists/other specialists; 89% patients enrolled by cardiologists	Internists, primary care physicians, cardiologists, and electrophysiologists; 80.5% of patients enrolled by cardiologists/electrophysiologists	Primary care physicians, neurologists, cardiologists, electrophysiologists
Definition of AF	New onset AF < 3 months prior to baseline visit	New onset AF < 6 weeks prior to baseline visit; ≥6 months but ≤24 months for validation group (5000 pts) only in cohort 1	New onset AF + all AF episodes < 12 months prior to baseline visit; AF diagnosed by an implanted pacemaker or defibrillator allowed	Incident or prevalent AF	New onset AF < 6 months prior to baseline visit
New onset AF	100%	30%	N/A	4.7%	76%
History of anticoagulant therapy	Patients excluded if with the history of VKA therapy > 60 days	Patients included regardless of prior or current VKA use	Patients included regardless of prior or current VKA use	Patients included regardless of prior or current VKA use	Previous VKA treatment allowed; Initiation or transition to NOAC < 3 months
Stroke risk scales	$CHA_2DS_2VASc \geq 1$ needed for inclusion	≥ 1 stroke risk factor by the physician discretion;$CHADS_2/CHA_2DS_2VASc$ scales not needed for inclusion	$CHADS_2/CHA_2DS_2VASc$ scales not needed for inclusion	$CHADS_2/CHA_2DS_2VASc$ scales not needed for inclusion	CHADS2/CHA2DS2VASc scales not needed for inclusion
Mean $CHADS_2$ score	1.9	1.9	N/A	2.3	2.0
Mean CHA_2DS_2VASc score	3.2	3.2	3.4	3.9	N/A

Enrollment timeframes with respect to NOAC approval dates	Sites selected only once NOACs available	Enrollment in time intervals irrespective of marketing authorization	Enrollment irrespective of marketing authorization	Enrollment irrespective of marketing authorization	Enrollment after NOACs approval
Overall OAC uptake	80%	62%	82%	76%	86%
Overall OAC uptake by drug type	32.3% VKA 47.7% NOACs	58% VKA 4% NOACs	76% VKA 6% NOACs	71% VKA 5% NOACs	22% VKA 64% NOACs
OAC uptake over time	Phase I (2011-2013) Europe - 64.1% Asia - 20.3% Middle East – 45.0% Phase II (2011-2014) Europe - 90.2% Asia - 57.4% Middle East/Africa – 79.8% North America – 78.2% Latin America – 84.9%	Cohort 1 (2009-11) - 57.5% Cohort 2 (2011-13) - 62.3% Cohort 3 (2013-14) - 67.5% Cohort 4 (2014-2015) -71% Cohort 5 – ongoing enrollment	N/A	N/A	N/A

AF = atrial fibrillation, GP = General practitioner, NOAC = non-vitamin K oral antagonist, OAC = oral anticoagulation, US = United States, VKA = vitamin K antagonist





Cohort design and data collection. Sequential cohort recruitment, with 'first patient in' December 2009.

Clinical Significance

- There is wide variety of registries on atrial fibrillation with evident differences in design and methodology.
- Registry data demonstrate that despite gradual improvement in anticoagulation rates worldwide, there are apparent regional differences and gaps in stroke prevention with approximately a third of atrial fibrillation patients not treated in accord with guidelines.
- Remote mortality of atrial fibrillation patients is relatively high, while guideline-adherent antithrombotic therapy significantly reduces thromboembolism and improves survival.

[DO NOT TYPESET THE TEXT BELOW]

Highlights

- This paper reviews past and currently ongoing atrial fibrillation (AF) registries.
- Main focus is on antithrombotic treatment patterns for stroke prevention.
- Design, strengths and limitations of various AF registries are discussed.
- Up-to-date situation on AF thromboprohylaxis worldwide is provided.
- Gaps in AF guideline-adherent antithrombotic therapy were identified and described.